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Title page

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Abstract

Deaths of home-care patients with coronavirus disease (COVID-19) have become a social problem. One of their causes is hypoxemia without dyspnea which delays seeking medical attention.

This was a retrospective study including patients registered in the COVID-19 Registry Japan, in which hospitalised patients with COVID-19 in 227 participating healthcare facilities were enrolled. The enrolled patients were divided into two groups: non-dyspneic patients with a peripheral capillary oxygen saturation (SpO_2) ≤93% on admission (the hypoxemia without dyspnea group) and non-dyspneic patients with an SpO_2 >93% (the control group). We conducted a multivariate logistic regression analysis to identify the factors associated with hypoxemia without dyspnea.

21544 patients were enrolled, 1035 (4.8%) patients were in the the hypoxemia without dyspnea group, and 20509 (95.2%) patients were in the control group. The median respiratory rate (RR) of the hypoxemia without dyspnea group was higher than that of the control group (31/min vs. 18/min, p <0.001). Age >65, male, body mass index >25, smoking, chronic obstructive pulmonary disease, other chronic lung disease, and diabetes mellitus were the independent factors associated with hypoxemia without dyspnea. Patients with those background should be closely monitored. RR is an

important indicator of hypoxemia, even in the absence of dyspnea.

Keywords: COVID-19, silent hypoxia, risk factors, respiratory rate, registry

1. Introduction

The main symptoms of COVID-19 are fever and respiratory symptoms [1]. Despite the absence of dyspnea, some patients with COVID-19 may have markedly reduced oxygen saturations, measured using pulse oximetry. This is referred to as “silent hypoxia” [2]

In Japan, every time there was a major COVID-19 wave, the medical facilities became overwhelmed, resulting in a rapid increase in the number of patients receiving treatment at home. As a result, several deaths were registered among the home care patients, which have become a social problem.

One of the causes of the death of home care patients with COVID-19 is silent hypoxia because the absence of difficulity of brathing despite the presence of hypoxemia delays seeking medical attention. Furthermore, patients with both COVID-19 and silent hypoxia are known to have poor outcomes [3]. Therefore, hypoxemia among patients with COVID-19 without dyspnea should be identified and monitored carefully. In this study, we identified the risk factors for hypoxemia among patients with COVID-19 without dyspnea.

2. Material and Methods

2.1. Study design

This was a retrospective study including patients registered in a nationwide Japanese registry, the COVID-19 Registry Japan (COVIREGI-JP). In this registry, patients who were diagnosed with COVID-19 (positive severe acute respiratory syndrome coronavirus-2 rapid antigen or polymerase chain reaction test) and hospitalized in the 227 participating healthcare facilities were enrolled. Research collaborators in each facility manually input the data into the registry by referring to the medical records. The study protocol was reviewed and approved by the Ethics Committee of the Center Hospital of the National Center for Global Health and Medicine (NCGM) (NCGM-G-004147-00), after a document on an opt-out policy for potential participants and/or their relatives was uploaded on the website of the Center Hospital of the NCGM. This study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Patients

Of the patients registered in COVIREGI-JP, we enrolled patients with COVID-19 who were non-dyspneic and who were hospitalized between January 1, 2020 and March 31, 2021. The enrolled patients were divided into two groups: non-dyspneic patients with a peripheral capillary oxygen saturation (SpO_2) ≤93% on admission (the hypoxemia without dyspnea group) and non-dyspneic patients with an SpO_2 >93% (the control group) [4]. Patients below 20 years old, patients whose SpO_2 was measured while they were receiving oxygen, or patients who had altered mentation, defined as P

or U on the Alert, Voice, Pain, Unresponsive (AVPU) scale, were excluded [5].

2.3. Statistical analysis

Categorical variables are presented as count (%), and continuous variables are presented as median and interquartile range (IQR). Fisher's exact test was used for categorical variables, and the t-test was used for continuous variables. To identify the factors associated with hypoxemia among patients with COVID-19 without dyspnea, we conducted a multivariate logistic regression analysis and obtained the adjusted odds ratio (OR) with 95% confidence intervals (CIs). Age, sex, body mass index (BMI), smoking, drinking, and comorbidities were independent variables. These variables were limited to those that could be obtained via telephone interviews by health center personnel. All analyses were performed using EZR ver. 1.54 [6].

3. Results

In total, 21544 patients were enrolled. Of these, 1035 (4.8%) patients were in the hypoxemia without dyspnea group, and 20509 (95.2%) patients were in the control group. The patients' backgrounds on admission and the outcomes are shown in **Table 1**. The median respiratory rate (RR) of the hypoxemia without dyspnea group was higher than that of the control group (31/min vs. 18/min, p <0.001). The median SpO_2 in the hypoxemia without dyspnea group was lower than that in the control group (91% vs. 97%).

The odds ratios and 95% confidence intervals of the factors associated with hypoxemia without dyspnea from the multivariable logistic regression analysis are shown in **Table 2**. The

hypoxemia without dyspnea was associated with age >65 years (95% CI: 2.920–4.350, p <0.001), male sex (95% CI: 1.070–1.600, p = 0.0087), BMI >25 kg/m^2 (95% CI: 1.160–1.600, p <0.001), smoking history (95% CI: 1.010–1.500, p = 0.036), chronic obstructive pulmonary disease **(**COPD) (95% CI: 1.300–3.100, p = 0.002), other chronic lung disease (95% CI: 1.060–3.400, p = 0.031), and diabetes mellitus (CI: 1.240–1.850, p <0.001).

4. Discussion

One of the most important findings in our study was that age >65 years, male sex, BMI >25 kg/m^2, smoking history, COPD, other chronic lung disease, and diabetes mellitus were independent factors associated with hypoxemia without dyspnea. Patients with COVID-19 having one of those characteristics may have hypoxemia and remain non-dyspneic. Thus, close monitoring of such patients is neccessary. Specifically, they should be provided transcutaneous oximeters so that they can self-monitor their SpO_2 regularly. Knowledge of the risk factors of hypoxemia among patients with COVID-19 without dyspnea will ease their identification and monitoring at health centers.

This study also revealed that the mean RR in the hypoxemia without dyspnea group was significantly higher than that in the control group (31/min vs 18/min, p <0.001). This finding implies that tachypnea is an important indicator of hypoxemia, even in the absence of dyspnea. Besides, RR is an indicator of a severe derangement in many body systems, not just the respiratory system [7]. As such, it is important for patients with COVID-19 and their families to know how to predict hypoxemia even without transcutaneous oximetry; this will ensure prompt medical attention before the disease

becomes severe.

This study had several limitations. First, this study was conducted in Japan, and thus the findings may not be generalizable to other countries. Second, the median SpO_2 in the hypoxemia without dyspnea group was 91%. It is likely that patients with COVID-19 who were very distressed could not complain of dyspnea. Therefore, patients with severe disease may have been enrolled in the hypoxemia without dyspnea group. Third, patients with COPD or chronic lung disease rarely complain of dyspnea, even in the presence of hypoxemia. Thus, it is difficult to determine whether the absence of dyspnea was due to silent hypoxia or to the original lung disease. Forth, only hospitalized COVID-19 patients were included in this study. Thus, home-care patients were not evaluated in this study. Lastly, the method of SpO_2 measurement was not standardized among the facilities.

Authors' contribution

Yutaro Akiyama: Conceptualization, Methodology, Formal analysis, Investigation, Writing-original draft preparation. Shinichiro Morioka: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing-original draft preparation, Writing review and editing, Visualization, Supervision, Project administration. Yusuke Asai: Methodology, Formal analysis, Data Curation. Lubuna Sato: Conceptualization, Writing review and editing. Setsuko Suzuki: Data Curation, Writing review and editing. Sho Saito: Conceptualization, Data Curation, Writing review and editing. Nobuaki Matsunaga: Data Curation, Writing review and editing. Kayoko Hayakawa: Conceptualization, Methodology, Writing review and editing. Norio Ohmagari: Conceptualization, Writing review and editing, Supervision.

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Conflict of Interest

All authors report no conflicts of interest relevant to this article.

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Tables

Table 1. Patients' demographics, and outcome

<Demographics>	Sub-categories	Total	the hypoxemia without dyspnea group	Control group
Sex (6 missing)	Male	11675 (54.2%)	597 (57.7%)	11078 (54.0%)
	Female	9861 (45.8%)	437 (42.3%)	9424 (46.0%)
Age, years	Median [IQR]	56 [39, 73]	73 [64, 84]	55 [38, 72]
Age (groups), years	20–64	13172 (61.1%)	271(26.2%)	12901(62.9%)
	≥65	8372 (38.9%)	764 (73.8%)	7608 (37.1%)
Ethnicity	Japanese	20559 (95.4%)	1011 (97.7%)	19548 (95.3%)
	Others	985 (4.6%)	24 (2.3%)	961 (4.7%)
Smoking history (3560 missing)	Former or current	7672 (42.7%)	397 (48.2%)	7275 (42.4%)
	Never	10312 (57.3%)	427 (51.8%)	9885 (57.6%)
Alcohol consumption (4982 missing)	Daily or occasional	9135 (55.2%)	353 (46.8%)	8782 (55.6%)
	Never	7427 (44.8%)	402 (53.2%)	7025 (44.4%)
Body mass index (3837	≤25	12007 (67.8%)	509 (63.4%)	11498 (68.0%)

missing), kg/m^2				
	>25	5700 (32.2%)	294 (36.6%)	5406 (32.0%)
Comorbidities[a]	Any	3632 (16.9%)	85 (8.2%)	3547 (17.2%)
	No	17912 (83.1%)	950 (91.8%)	16962 (82.7%)
Body temperature[b] (3 missing), °C	Median [IQR]	38.5 [36.5, 37.4]	37.4 [36.8, 38.0]	38.6 [36.5, 37.4]
Respiratory rate[b] (5883 missing), breaths/min	Median [IQR]	18 [16, 20]	31 [17, 22]	18 [16, 20]
Days from onset of symptom to hospitalization (3124 missing)	Median [IQR]	4.9 [2, 7]	5.4 [2, 8]	4.9 [2, 7]
Oxygen administration during admission and modality (5 missing)	No oxygen therapy	17021 (79.0%)	284 (27.4%)	16737 (81.6%)
	Oxygen therapy	4518 (21.0%)	751 (72.6%)	3767 (18.4%)
	IVT/ECMO	278 (1.2%)	57 (5.1%)	221 (1.0%)
Outcome (5 missing)	Death	552 (2.6%)	88 (8.5%)	464 (2.3%)
	Discharged to home or transferred to facilities	20987 (97.4%)	944 (91.5%)	20043 (97.7%)

Abbreviations: IQR, interquartile range; IVT, Invasive ventilation therapy; ECMO, Extracorporeal membrane oxygenation.

[a]Including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, paralysis, dementia, chronic lung disease, bronchial asthma, liver dysfunction, renal dysfunction, solid tumor, leukemia, lymphoma, collagen disease, human immunodeficiency virus infection, and acquired immunodeficiency syndrome.

[b]On admission

Table 2. Factors associated with hypoxemia among patients with COVID-19 without dyspnea—Multivariable logistic regression (n = 13668)

Variables	Odds ratio	95% CI	*p*-value
Age (>65 years)	3.56	[2.92, 4.35]	<0.001
Male sex	1.31	[1.07, 1.60]	0.0087
Body mass index (>25 kg/m^2)	1.39	[1.16, 1.60]	<0.001
Smoking history	1.23	[1.010 1.50]	0.036
Drinking alcohol	0.848	[0.702, 1.02]	0.851
Myocardial infarction	1.1	[0.664, 1.83]	0.706
Congestive heart failure	3.44	[0.765, 15.5]	0.107
Peripheral vascular disease	0.643	[0.323, 1.28]	0.207
Cerebrovascular disease	1.15	[0.852, 1.54]	0.367
Chronic obstructive pulmonary disease (COPD)	2.01	[1.30, 3.10]	0.002
Chronic lung disease (excluding COPD)	1.9	[1.06, 3.40]	0.0305
Bronchial asthma	0.997	[0.671, 1.48]	0.987
Hypertension	1.18	[0.972, 1.42]	0.095
Hyperlipidemia	1.19	[0.958, 1.47]	0.118

Severe renal dysfunction/Hemodialysis	0.704	[0.352, 1.41]	0.320
Liver dysfunction	0.975	[0.594, 1.60]	0.919
Diabetes mellitus	1.51	[1.24, 1.85]	<0.001

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval